# Bone marrow transplants do not help in breast cancer

Scott Gottlieb, *New York*

Preliminary results released early from 4 ongoing clinical studies of breast cancer treatments indicate that high-dose chemotherapy followed by bone marrow transplantation may not significantly improve survival, although positive results from a fifth trial, also released early, seem to suggest otherwise. For almost a decade, ultrahigh doses of chemotherapy followed by a bone marrow transplant, to rescue the destruction of the immune system caused by such regimens, has become a preferred treatment in the United States for women with recurrent or advanced breast cancer.

Thousands of women have demanded the procedure. Insurance companies routinely pay for it, even though there is no proof of its effectiveness. Preliminary research released by the National Cancer Institute reflecting 4 of the 5 long-awaited studies of 2,100 women in the US, Scandinavia, and France, found no difference in survival between patients who had high-dose chemotherapy with transplants, and those who had lower doses of chemotherapy.

The fifth study, from South Africa, did find a benefit in patients with positive lymph nodes, suggesting that the treatment might help some women. In this study, 154 women who received the high-dose chemotherapy plus a transplant suffered fewer cancer relapses in the 5-year period following the procedure. After more than 5 years of follow-up, 17% who received transplants had died, as compared with 35% in the other group.

Taken together, the 5 studies are not scheduled to conclude for another 3 to 5 years. Dr Alan Lichter, president of the American Society of Clinical Oncology, said in a conference call with reporters that the lack of conclusive findings thus far in the follow-up suggests that if the procedure does eventually turn out to have a benefit, it will be small. Dr Lichter said, however, these findings might enable better clinical studies, since the early results might "dispel the concern that if you're in a trial and are not on the high-dose arm, you're really missing the boat."

Summaries of the 5 studies are available on the Internet at www.asco.org.

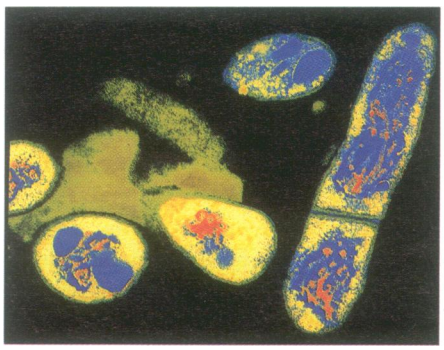
# Researchers find genetic basis for susceptibility to mycobacteria

Deborah Josefson, *San Francisco*

Genetics may explain why some people are more susceptible to non-tuberculous mycobacteria infections than others. Researchers at INSERM (National Institute for Medical Research), in Paris, France, investigated the clinical syndrome of disseminated non-tuberculous mycobacterial infection, in which otherwise healthy individuals without detectable immunodeficiency develop overwhelming infections with mycobacteria that are normally not virulent (*Nature Genetics* 1999; 21: 370-8). They uncovered a genetic basis to an underlying susceptibility to infection—one of the few times that discrete, heritable, and spontaneous mutations have been found responsible for making someone vulnerable to a specific microorganism.

*Mycobacteria tuberculosis* and *M. leprae*—the organisms that cause tuberculosis and leprosy—are the most pathogenic mycobacteria, although most bacteria in their class are relatively harmless. Rare individuals, however, develop disseminated infections with normally non-virulent non-tuberculous mycobacteria. People with the genetic defect can also develop fatal infections after vaccination with *Bacille Calmette-Guérin* (BCG).

The INSERM researchers studied several families with idiopathic reactions to vaccination with BCG or disseminated non-tuberculous mycobacterial infection, including 18 people from 12 unrelated families. From previous investigations, it was known that the receptor for interferon gamma—a cytokine with a central role in combating bacterial, viral, and parasitic infections—was implicated.



AP photo/Rich Harrington

A genetic defect underlies susceptibility to mycobacterial infection

When researchers examined the DNA region encoding the interferon receptor in affected families, they found homozygous mutations in the region, accounting for an autosomal recessive mode of inheritance in some families.

The importance of interferon in combating non-tuberculous mycobacterial infections was underscored by the finding that mutations in genes encoding interleukin 12 (a cytokine that stimulates various cells to secrete interferon) also increased susceptibility. The researchers also found heterozygous mutations in the receptor gene that were inherited in an autosomal dominant manner. This is the first time that autosomal dominant inheritance to a particular pathogen has been found.

Further analysis of these receptor gene mutations showed that they produced a functionally deficient receptor that migrated to the cell surface normally but was unable to respond to interferon. The mutated receptor clogs the cell surface and competes with the normal receptor for interferon binding, further crippling the response to interferon.